IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Van Der Berghe et al.
Serial No.: 10/528,802 Art Unit: 1644
Filed: 23 March 2005

Examiner: Haddad, Maher

Attorney's d ocket: BERGHE 1

Title: Methods and preparations for curing critically ill patients

DECLARATION OF PROFESSOR ALISON FREIFELD, MD, UNDER 37 C.F.R. § 1.132

I, Alison Freifeld, declare and state as follows:

1. I hold an MD degree. I am currently employed as Director of the Immunocompromised Host Infectious Disease Program at the Department of Medicine, University of Nebraska Medical Center, where I am Professor of Medicine.

2. I have reviewed and understood the Office Communication of August 23, 2007. (not yet)

3. The Examiner ranks bone marrow transplants (BMT) and hematopoietic cell transplantations (HCT) along with other types of transplantation.

4. The information summarized below is my understanding of the differences between solid organ transplantations and haematopoietic cell transplantations.
References to text books are provided for several factual statements presented herein with references to the following books:
    1. Infectious Diseases, edited by Amrstrong and Cohen (1999), Vol.1, section 4 Chapter 3: Solid Organ eds. Dunn and Action, Chapter 4: Blood and Marrow transplantation eds. Bowden.
    2. Hematopoitic Cell Transplantation, 2nd edition by Thomas, Blume and Forman (1999).

5. The complications arising after solid organ transplantation and blood marrow transplantation (BMT)/hematopoietic cell transplantation (HCT) are distinct. One of the main differences is the high occurrence of post-operative infections associated with the operative site in solid organ transplantations. Post-operative infections generally appear to localize at the site of the graft implantation, which may be related to operative trauma. For example renal transplant recipients typically develop urinary tract infections (UTI); hepatic, small bowel and pancreas transplant recipients typically develop intra abdominal abscesses whereas cardiac and lung transplant recipients develop mediastinitis, bronchitis or pneumonia.

6. Wound and periallograft infection is a frequent and serious complication of solid organ transplantations that does not occur in recipients of BMT/HCT. These infections can be divided into superficial infections i.e. infections above the fascia; deep infections i.e. below the fascial closure and within the body cavity in which the transplant operation was performed and combined infections. The total incidence of wound infections ranges from 1 – 2% in renal transplant recipients and 25-30% in pancreas and small bowel transplant recipients. Deep wound

infection in for example renal, pancreas, hepatic or small bowel recipients are very serious events that are often associated with systemic sepsis or pseudoaneurysm formation at the site or vascular anastomosis. In some cases this this process can be limb-threatening as the iliac arteriovenous system is used for transplantation.

7. In contrast one of the most prevalent complications arising following blood marrow transplantation (BMT)/hematopoietic cell transplantation (HCT) is graft versus host disease (GVDH). GVDH is a common complication in blood marrow transplantation (BMT) and hematopoietic cell transplantation (HCT), but is rarely seen in solid organ transplants.

8. Furthermore, deposition of complement split product C4d along the capillaries of an organ graft has been suggested as a marker for humoral rejection of organ allografts in solid organ transplant recipients (reviewed in Platt, J. (2002) C4d and the Fate of Organ Allografts, J Am Soc Nephrol 13: 2417-2419). However, the mere presence of C4d does not per se imply increased risk of humoral rejection. C4d is observed after rhMBL activation of the complement system,.

9. As have been described herein solid organ transplantations and bone marrow or hematopoietic cell transplantations are two distinct scenarios, which raise different difficulties. It is not obvious to adapt teachings from one type to the other due to the differences.

10. I further declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 21 January 2008 Signature: Alison Freifeld MD

(Alison Freifeld, MD)